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Human population of the Balearic Island: the case of Chuetas and Ibizans*

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Introduction

The Balearic Archipelago is located in the western Mediterranean Sea, near the eastern coast of the Iberian Peninsula. It is composed of three major islands, Majorca, Minorca, and Ibiza. Due to their geographical position in the Mediterranean Sea, the Balearic Islands have been settled throughout their history by people of different populations. Merchant Greek and Carthaginian ships sailed to trade with the aboriginal Balearics. Various civilizations have left their mark on the islands, including the Phoenicians, Greeks, Carthaginians, Romans, Vandals, Byzantines, and Moors. In 654 BC, the Phoenicians made Ibiza (Ibusim) an important commercial centre. In 123 BC, Romans conquered Majorca and made it part of Roman history for five and a half centuries. The Western Byzantines became the new conquerors in 534 AD, until they were ousted by the Muslims in the 8th century. In 902 AD, the entire archipelago was annexed to the Caliphate of Cordoba. At the end of 1229, Jaume I 'the Conqueror', the Catalan King of the Crown of Aragon, annexed Majorca to his kingdom. The other islands were also conquered and occupied by the Catalans in the following years, thus forming the basis of the present day islands. At the end of the 15th century, the Balearics were united with the Kingdom of Spain as part of the political union of Castilla and Aragon.

The Balearic Islands offer an opportunity to observe genetic diversity based on reproductive isolation: geographical isolation (Ibiza population), and cultural isolation (Chuetas, descendents of Majorcan Jews). The three main islands have different histories of settlement. Majorca and Minorca have similar megalithic monuments and were occupied by the same people in historical periods. Ibiza is different from the two other islands, not only in its landscape and vegetation but also in the origin of the founding settlements. Ibiza was an important Carthaginian colony, evidence of which can be seen in archaeological remains that have been found. The Ibizan population was reproductively isolated and has thus received little gene flow from outside. Although the scarcity of available data concerning population size (e.g., 3000 in 1392; 9596 in 1652) does not indicate a drastically low number of people, the incidence of infectious diseases, such as the plague and malaria, considerably reduced the effective size of the population. Moreover, the demographic structure and marriage practices highlight the existence of genetic drift on this island. The rural population had a dispersed township with small properties, and marriages were suitably arranged so as not to divide the lands, and in numerous cases they were carried out between relatives. This apparent reproductive isolation was disturbed by the 1970s tourist influx that considerably increased the total population.

The genetic structure of the present-day Jewish population is the outcome of a common ancestral gene pool and the admixture with people among whom the Jews lived. A number of Jews living in the Middle East moved west in 70 AD after the Romans destroyed Jerusalem. The first Jewish communities were established in

Majorca in the 1st century AC. They reached a period of great development and scholarly achievement throughout

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Spain and Portugal. The Sephardic Jews, who were descendants of Jews whose ancestors lived in the Iberian Peninsula, were thrown out of Spain in 1492 (Sephardi meaning 'from Sepharad', which is Hebrew for 'Spain'). Those who stayed in Spain were forced to convert to Christianity between 1391 and 1497. After the expulsion edict they left and settled mainly in North Africa, the Balkans and Eastern Mediterranean countries. The Spanish Inquisition began its activities in

Majorca in 1488 and as a result, 769 converted individuals were judged during the following 50 years. In 1678 and 1691 the Spanish Inquisition acted again in Majorca conducting an 'auto de fe' (act of faith), which condemned 240 individuals belonging to this community. The descendants of this Majorcan Jewish population, the Chuetas, were secluded by their immediate neighbours and have shown a strong endogamic behavior from this period until nowadays. This isolation almost exclusively affected the individuals with the 15 typical surnames belonging to the accused people in the last Inquisition.

Genetic variation in the population of Ibiza (Spain) *vs*. other Balearic Islands by several genetic population markers

Allele frequencies were calculated for the following blood group and serum systems: ABO, Rh, MNSs, P, Lewis, Duffy, Kell, ORM, GC, TF, PI, and HP. The allele frequencies from Ibiza were compared with those from other Balearic Islands (Majorca and Minorca) and with related European and North African groups. Data revealed that Ibiza is genetically different from the other Balearic populations [19]. For some markers the Ibiza population seems to be closer to North African, Middle Eastern, and other insular Mediterranean populations than to European populations. It is thought that this might be due to the different origin of the Ibiza population.

Mitochondrial DNA (mtDNA) is a double-stranded, circular, covalently-closed molecule of 16569 bp in humans that is inherited as a haploid from the mother without recombination and/or segregation. Its high mutation rate (2-4% per million years) leads to a high degree of variability between individuals. Thus mtDNA is a good tool for studying the genetic structure of populations [3]. The first human population studies were performed by mtDNA restriction enzyme analyses, and they revealed differences between the four ethnic groups (Caucasian, Amerindian, African, and Asian). In the Balearic Islands, the study of the genetic structure of these populations through restriction fragment length polymorphism (RFLP) analysis of their mtDNA by using 5 restriction enzymes showed similar results to previous studies of the genetic structure of the Balearic population using hematologic polymorphisms [14,19]. The genetic homogeneity is higher in Majorca than in Minorca and Ibiza. This result is due to the high frequency of haplotype 1 in this population. In Minorca, with the most heterogeneous population, the most frequent haplotype is also 1, although there are other haplotypes in polymorphic frequencies as well as a new one, 150 (8%). Ibiza had only four haplotypes, with haplotype 1 also having the highest frequency. The genetic diversity between populations is about seven fold higher for Majorca–Ibiza and Minorca–Ibiza than for Majorca–Minorca, which indicates a genetic differentiation of Ibiza with respect to Majorca and Minorca (Table 1 / Table 1 IM 1998).

Table 1. Frequencies (in percentage) and haplotypic diversities of the different haplotypes detected in the Balearic Islands [3]

		Majorca		*Minorca*		*Ibiza*		*Chuetas*	
Types of mtDNA	*Haplotype*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
1	2-1-1-1-1	44	84.6	28	56.0	25	50.0	39	72.2
2	3-1-1-1-3	0	–	0	–	5	10.0	0	–
6	2-1-2-1-1	2	3.8	7	14.0	0	–	7	13.0
7	3-1-1-1-1	1	1.9	0	–	0	–	0	–
8	1-1-1-1-1	0	–	3	6.0	0	–	0	–
11	2-2-3-1-5	0	–	0	–	1	2.0	0	–
18	2-3-1-4-9	3	5.8	0	–	19	38.0	4	7.4
22	2-3-1-1-9	1	1.9	0	–	0	–	0	–
24	2-1-1-4-2	0	–	1	2.0	0	–	0	–
39	2-1-4-1-1	0	–	0	–	0	–	1	1.8
56	2-1-1-1-6	0	–	1	2.0	0	–	0	–
57	2-3-1-4-13	1	1.9	6	12.0	0	–	2	3.7
59	2-1-1-1-20	0	–	0	–	0	–	1	1.8
150	2-1-2-1-6	0	–	4	8.0	0	–	0	–
Total		52	100	50	100	50	100	54	100
h		0.284		0.655		0.607		0.444	

h, haplotypic diversity.
N, number of individuals.

Considering the different haplotypes, the most characteristic in Majorca are Caucasians (mainly haplotype 1 and also haplotypes 6 and 18), although the presence of haplotype 7 suggests an Arabian/African genetic contribution to this population. Haplotype 7 could have been introduced into Majorca by the Arabians, who lived in the islands for around five hundred years. This haplotype is not as frequent in Majorca (1.9%) as it is in Arabian communities (4.8%) [21] but it is in the same order as in other Caucasian groups such as the Romans (1.1%) [2] and Askenazi Jews (1.3%) [21]. In Ibiza, the exceptional fact is the high frequency of haplotype 18 (38%). This is considered an ancient Mediterranean mtDNA type found at a maximum frequency of 12% in the centre and south of the Italian peninsula and Sicily. We can say that, in Ibiza, two mtDNA lineages are present, one represented by haplotype 1 and the other by haplotype 18 [3].

The HLA system was another marker extensively studied from an evolutionary perspective. The region contains a number of closely linked genes whose products control a variety of functions concerned with the regulation of immune responses. Genes comprising the major histocompatibility complex (MHC) play a central role in governing the immune response of vertebrates. A great deal of information has been revealed on the molecular biology and physiology of these loci, but three features—the high polymorphism, tight linkage among the loci, and the nonrandom association of alleles—make the system of particular interest from the perspective of population genetics. Information on the dynamic evolutionary forces that have acted on a locus can be inferred from the number and distribution of alleles that it carries. Five loci from the HLA region of the human MHC (HLA-A, -B, -Cw, -DRB1 and -DQB1 loci) have been examined [5]. Some peculiarities were observed in the distribution of common haplotypes among the three main Balearic Islands. The Ibizan population was genetically different from the other Balearic populations, with a high frequency of some haplotypes, for example, A29-Cw*16-B44-DRB1*07-DQB1*03; A1-Cw*07-B8-DRB1*03-DQB1*02. We also found a new haplotype, A25-Cw*12-B39-DRB1*11-DQB1*03 (3.5%), in Ibizans and a more limited variability in the HLA alleles that were expressed, perhaps because of genetic isolation. The genetic diversity of the populations from Majorca and Minorca were similar and more related to the mainland Spanish population. Interestingly, our results show a frequent haplotype, A25-Cw*12-B39-DRB1*11-DQB1*03, found in Ibiza (3.5%), that is not found in other populations and might be specific to the original population of the island (Founder effect) (Figure 1 / Figure 2; [5]). We can speculate about its Phoenician/Carthaginian origin although the available data does not support this as a similar haplotype was not found in populations belonging to countries that occupy the geographic territory from where the Phoenicians came [5]. The alleles A25 and B39 are relatively frequent in neighboring populations such as Italians (3% and 2%), Portuguese (1.9% and 2.9%), Spaniards (1.5% and 1%) and French (1.4% and 2.5%), and rare in other Mediterranean Island populations such as Corsica (1% and 0.5%) and Sardinia (0% and 1%). A30-Cw*05-B18, frequently found in Spaniards and defined as of Iberian Paleo-North African origin [1,15], was not found in Ibizans (the most southern island of Balearic Islands) and was found at a relatively low frequency in Majorcans (2%) and Minorcans (1.5%). Interestingly, it had a very high frequency in the neighboring Mediterranean regions such as Algeria, where it was the most frequent haplotype [4], Sardinia (12.5%) [8], and in the Basque region (3.7%) (Figure 1 / Figure 2; [5]).

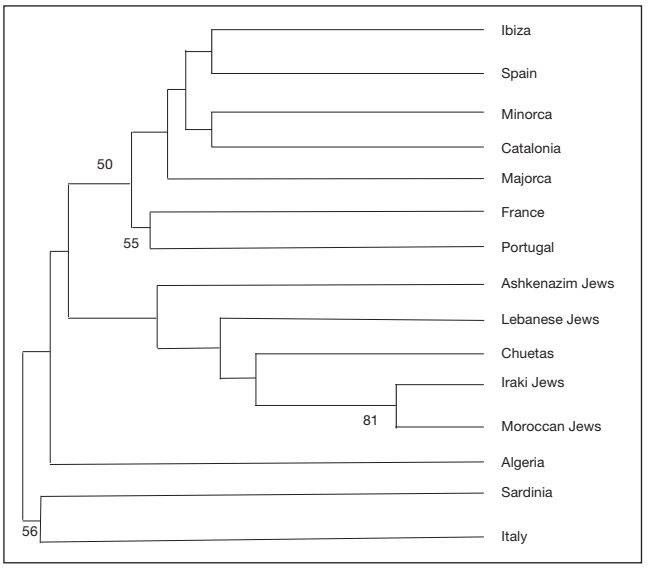

Figure 1. Tree base on Standard Genetic Distances using the frequencies of HLA-A, -B and -DRBI. Only the bootstrap above 50 are represented.

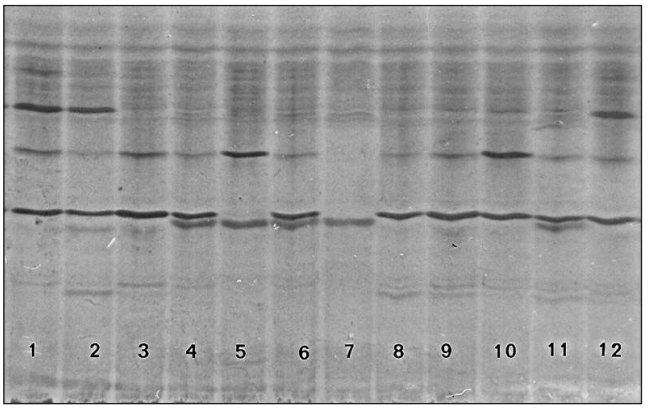

Figure 2. Haptoglobin subtypes. Genotypes in lines 1,2,12:1S-2FS; lines 3,8,9: 2FS; lines 4,6,11:2FS-1F; line 5:2SS-1F; line 7:1F; 10:2SS-FS.

Genetic variability of Chuetas (Majorcans Jews): a comparative study

A study of the Chueta population has been carried out to establish the genetic relationships between the Chuetas and other Jewish and non-Jewish circum Mediterranean populations by several population-variability markers.

Picornell, et al. (1997) studied the Chueta community (identified by on of the 15 surnames: Aguiló, Bonnin, Cortés, Forteza, Fuster, Martí, Miró, Picó, Piña, Pomar, Segura, Tarongí, Valentí, Valleriola and Valls) using blood groups ABO, MNSs, P, Ph, Kell (KEL), and Duffy (FY); red cell enzymes glucose 6-phosphate dehydrogenase (G6PD), 6-phosphogluconate dehydro-

genase (PGD), acid phosphatase (ACP1), phosphoglucomutase 1 (PGM1), glyoxalase 1 (GLO1), and adelynate kinase (AK1); serum proteins haptoglobin (HP) and group specific component (CG). The results indicate that most of the Jewish communities resemble each other and other Middle Eastern populations, because of their common origin, but they also have affinities with their host peoples. The Chueta population is midway between non-Jewish populations of the western Mediterranean and some Jewish populations, especially European ones (Polish, Askhenazi, and Sephardic Jews), although they are closer to non-Jewish populations [16]. (Figure 2 / Figure 3, Picornell article, 1997). As expected, the Samartians are clearly separated, and it is interesting to see the proximity of the Ethiopian populations and Ethiopian Jews. In fact, the Ethiopian Jews were converted and, so they have the same genetic structure as the rest of the Ethiopians.

Most mtDNA variation studies have employed one of two methods: direct sequencing of the rapidly evolving control region (CR), or digestion of the entire molecule by means of standard sets of restriction enzymes. Richards et al. (1996) produced a phylogenetic network of sequences from the first hypervariable segment (HVRI) of the CR. The analysis of the mtDNA hypervariable region segment I sequence (HVRI) in three insular Balearic populations (Majorca, Minorca, and Ibiza) and the Chueta community showed that the incidence of unique haplotypes was very low, especially in Ibiza and the Chuetas. A remarkable observation in the Chueta community was the high frequency (23%) of preHV-1, a Middle Eastern lineage that is closely related, though not identical, to many others found at high frequencies in different Jewish populations. The presence of this haplogroup convincingly supported again the Jewish origin of the Chueta community. The studied populations showed a reduced African contribution, and no individuals were detected with North African haplogroup U6, indicating a lack of maternal contribution from the Muslim settlement to these populations [18].

The study of the genetic variability in the Chueta (Majorcan Jews) and the Balearic (Majorca and Minorca Islands) populations was carried out using a multiplex system containing the nine tetrameric short tandem repeats (STRs) D3S1358, vWA, FGA, D8S1179, D21S11, D18S51, D5S818, D13S317 and D7S820, again demonstrated that the Chueta population has remained isolated because intermarriage with non-Jews did not take place until the middle of the twenty century, which has resulted in it being a small inbred community [24].

The Chueta community has a particular history, which is different from other European Jews and which probably molded their genetic structure. The social discrimination to which they were subjected and their adherence to tradition restricted the influx of genes from the host population, but mixed marriages with local population could have taken place more easily than mixed marriages between other Jewish European populations and their host people where there were strict barriers of religion. Chuetas showed an admixture rate (50%) larger than rates found in other Sephardic Jewish populations but smaller than for instance the rate in Yemite Jews (71%) were conversions to Judaism from local people are known [17].

Differential maternal and paternal contributions to the genetic pool of Balearic Archipelago

It was observed in most studies that there is a different contribution of Y-chromosome and mtDNA haplotypes to the significant differences between populations, which can be explained by unequal involvement of males and females in the different admixtures. The expansion and loss of matrilines and patrilines can cause considerable fluctuation in the frequencies of mtDNA and Y-chromosome haplotypes (Helgason, et al., 2003). In general, lower levels of Y-chromosome diversity than mtDNA diversity are reported for the same population, and this reflects patrilocality and/or biased male reproductive success [11], although in some populations the inverse process is produced and matrilocality has also been considered [22].

We have compared the genetic diversity between Ibiza and the population of the other Balearic Islands and also between the Archipelago with respect to circum-Mediterranean populations. For such a comparison we studied autosomal and Y-chromosome STRs, as well as mtDNA sequence data analyzed from the same individuals. The analysis of 9 autosomal STRs (D3S1358, vWA, FGA, D8S1179, D21S11, D18S51, D5S818, D13S317, and D7S820) showed that Ibiza had significant differentiation with respect to other Balearic populations and also with respect to insular and continental populations from the Mediterranean area (Figure 3 / Figure 2; Tomàs article, 2006). Nevertheless, the results obtained from the analysis of eight Y-STRs (DYS19, DYS389I, DYS389II, DYS390, DYS391, DYS392, DYS393, and DYS385) showed a high level of genetic homogeneity for eight western Mediterranean populations. On the other hand, these populations did not show a compacted group when mtDNA diversity was analyzed, since they showed genetic differentiation among them. The analyses of haplotypes shared between populations indicated that mtDNA haplotypes have drifted to higher frequencies than the Y chromosome. The haplotypes of Y-STRs did not differ significantly between the Balearic Islands [23]. The results obtained for the genetic differentiation of the Balearic Archipelago indicate a clear differentiation of Ibiza Island with respect to the other Balearic populations, Majorca and Minorca, in autosomal and mtDNA markers. However, Ibiza does not show differences when Y-chromosome STRs are considered. Therefore, in this case, the Y-chromosome markers are less informative for tracing the history of the different Balearic populations [23]. We propose a maternal Carthaginian/Phoenician founder effect for the Ibizan population, in accordance with the history of the area, although this is difficult to confirm. Obviously, the genetic drift generated by this founder effect, as well as by the fact that Ibiza is a small island, has affected the genetic differentiation of Ibiza Island. This drift has affected mtDNA more than the Y chromosome. In diverse historic periods, the extremely poor economic situation promoted the exodus of men and created a very stable conserved matrilocal regime. One clear example, indicative of the few changes in the life of Ibizan women, is that the feminine wardrobe was not modified on the island until the end of the 1970s, whereas the masculine wardrobe changed, as on the other islands, according to the epoch. The Y-STRs

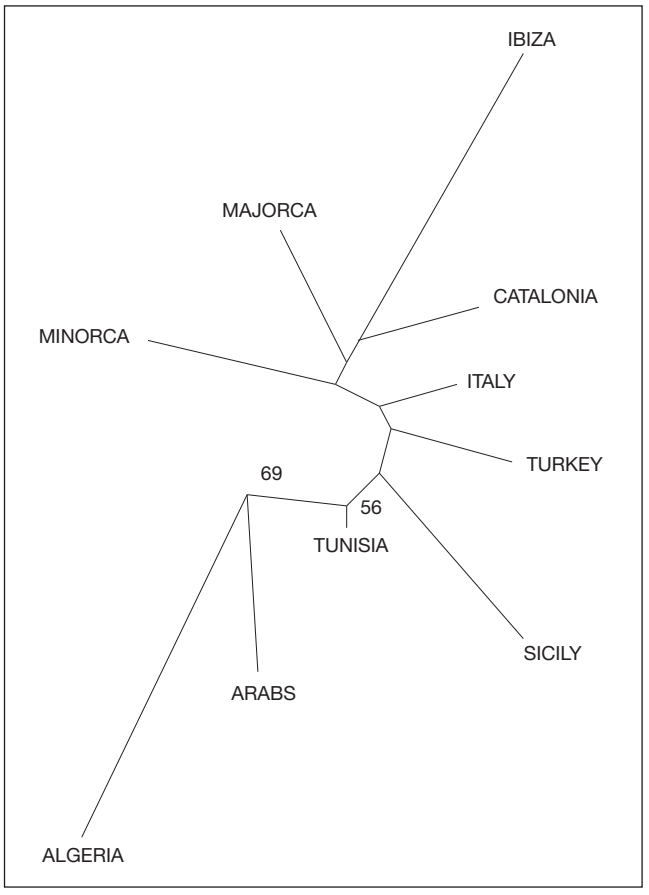

Figure 3. Tree base on Standard Genetic Distances using the frequencies of HLA-A, -B and -DRBI. Only the bootstrap above 50 are represented.

showed a high level of diversity and a strong homogeneity among western Mediterranean populations that could be related with numerous male displacements originated by wars and commercial relations. The founder effect and the high rate of consanguineous marriages could explain the genetic differentiation of the Ibizan population with respect to Majorca and Minorca, which is especially evident in the mtDNA.

Prevalence of hereditary hemochromatosis and familial Mediterranean fever in Jewish population: clinical implications

Hereditary hemochromatosis (HH) is an autosomal recessive trait, frequently found in Caucasian populations, in which the excess absorption of iron from the diet leads to severe organ damage. If the disorder is diagnosed before organ damage has occurred, reduction of body iron stores to normal will prevent organ disease and result in a normal life expectancy. Two mutations in the HFE gene (C282Y and H63D) were identified as being responsible for the disease [7]. Frequencies of HFE C282Y and H63D mutations have been analyzed worldwide. The C282Y mutation is most abundant in North European populations and in those of North European descent (allele frequencies of 5–10%). H63D has a much broader distribution, with high frequencies throughout Europe (10–30%), especially in the Mediterranean area, and moderate frequencies in North Africa, the Middle East, and parts of Asia (8–10%). In Spanish populations, high H63D frequencies are found (>15%). The distribution of the HFE C282Y and H63D mutations in Chuetas revealed that the H63D mutation was one of the highest frequencies (26.6%) described to date. The frequencies found in the literature in Ashkenazi Jews for the H63D mutation (approximately 9%) and non-Ashkenazi Jews (Oriental, Sephardic and Borth African) arround 12%, differ significantly from that found in Chuetas. An important question is why Chuetas have such a high frequency of the H63D mutation. The Chueta population has a particular history—different from other Jews—which has probably moulded their genetic structure. Despite their social isolation, their conversion to Christianity (15th century) allowed mixed marriages with the local population to take place more easily than in other European countries, where there were strict religious barriers between Jews and their host people. In fact, previous studies on classical and DNA genetic markers in Chuetas showed a substantial admixture rate (approximately 50%). Taking into account this previous genetic information for Chuetas, which indicated that they are a hybrid population between Sephardic Jews and Majorcans, we have calculated the H63D frequency expected in Chuetas. The frequencies found in Majorca and Sephardic Jews were 19.5 and 13.3%, respectively. This, combined with an admixture rate of 50%, means Chuetas should have a H63D prevalence of around 16%, which differs significantly from the observed value (26.6%). Therefore, we can discard the fact that the high frequency observed is only due to admixture (Matas, et al., 2006). Genetic drift seems to be the most probable cause for the H63D frequency found in Chuetas. Although there is no historical knowledge about the number of founders of the Chueta population, it is reasonable to assume that the number of Sephardic settlers on the Island of Majorca would have been low. In addition, this population suffered different bottlenecks throughout its history, mainly due to the pursuit of the Inquisition. These situations may have led to allelic frequencies different from those in ancestral populations. H63D homozygotes genotype must be considered because it confers an increased risk of iron overload and therefore genetic susceptibility to developing HH or to aggravating other diseases [12]. In population of the Balearic Islands diagnosed with HH, the homozygous C282Y genotype was the principal one involved in hereditary

Table 2. Genotype frequencies of C282Y and H63D mutations of HFE gene in the Balearic Islands

	Population			
Genotype	Mallorca N = 192	Ibiza N = 94	Minorca N = 113	Chuetas N = 71
+ / +	0.58	0.56	0.68	0.52
+ / C282Y	0.05	0.06	0.01	0
H63D / H63D	0.01	0.05	0.04	0.05
+ / H63D	0.35	0.31	0.27	0.43
C282Y/H63D	0.01	0.02	0	0

N = Number of individuals.

haemochromatosis (90%), whereas the other HH patiens were C282Y/H63D compound heterozygous and H63D homozygous (Table 1 / Table 2, Guix article) [9].

Familial Mediterranean fever (FMF) or recurrent polyserositis is a hereditary disease characterised by recurrent attacks of fever, transient peritonitis, pleuritis or synovitis, usually lasting from 1 to 3 days. The disease occurs predominantly in Jewish populations. The finding of a cluster of FMF patients exclusively among the Chuetas while the disease is unknown among non-Chuetas inhabitants of Mallorca, raised the question of their possible Jewish origin. The genotype of eight Chuetas FMF families showed that three of them had the S haplotype, which is specific for the North-African FMF Jewish patients. One family bore the S2 haplotype, which is also common among FMF Jews. Therefore, it is likely that at least part of these two populations (Chuetas and Jews) acquired the FMF gene defect from a common ancestor [6].

The human population of the Balearic Islands presents two interesting cases when studied from a genetic populational point of view: the Chuetas and Ibizans. In both, the founder effect determined by their origin and the existence of endogamy are the most out-standing aspects. In Ibizan population, a maternal and paternal differential contribution must be taken into account.

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